Contact Lens and Anterior Eye 47 (2024) 102091

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

journal homepage: www.elsevier.com/locate/clae

Platelet-rich plasma for treating dry eye disease – A systematic review and meta-analysis

Prince Kwaku Akowuah [a,1], Chukwuemeka Junior Obinwanne [b,1], Ebenezer Owusu [a,*], Sylvester Kyeremeh [c], Kwaku Bonsu [a], Lucy Akua Afriyie Karikari [d], Felicia Akyaa Akomeah [c], Ernest Kyei Nkansah [e], Emmanuel Kobia-Acquah [c,e]

[a] College of Optometry, University of Houston, Houston, TX, USA
[b] Cornea and Contact Lens Unit, De Lens Ophthalmic Family and Vision Care Centre, Abuja, Nigeria
[c] Department of Optometry and Visual Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[d] First Vision Eye Care and Medical Devices, Kumasi, Ghana
[e] Centre for Eye Research Ireland, Environmental Sustainability and Health Institute, Technological University Dublin, Dublin, Ireland

ARTICLE INFO

Keywords:
Dry eye disease
Platelet-rich plasma
Symptoms
Tear quality
Tear quantity

ABSTRACT

Purpose: Dry eye disease has public health and economic significance. Platelet-rich plasma is rich in anti-inflammatory agents and growth factors, both beneficial for ocular surface repair. This study aimed to conduct a systematic review and *meta*-analysis to summarize the benefits of platelet-rich plasma for treating dry eye disease and its adverse effects.

Methods: Prospective comparative studies using platelet-rich plasma as monotherapy for dry eye disease were included for efficacy assessment. Before-after studies were included for adverse events assessment. Data sources included PubMed, Google Scholar, Web of Science, and Scopus. A systematic review and *meta*-analysis protocol was pre-registered on PROSPERO (CRD42022347982). PRISMA guidelines were followed. The National Health Institute (NIH) quality assessment tool for before-after studies, the Cochrane risk of bias tool (RoB2), and the methodological index for non-randomized studies were used to assess the risk of bias. Heterogeneity was assessed using the I^2 statistic.

Results: 19 studies (10 comparative and 9 before-after) were included in the systematic review and *meta*-analysis. The occurrence rate of adverse effects was 2.6 % (95 % CI: 0.5 – 4.7). The pooled standardized mean difference (SMD) for dry eye symptoms was 0.81 (95 % CI: 0.25 – 1.37; $I^2 = 82$ %; $p < 0.00001$; $Z = 2.84$, $p = 0.004$); tear quality was 0.44 (95 % CI: 0.06 – 0.81; $I^2 = 67$ %; $p = 0.003$; $Z = 2.26$, $p = 0.02$); tear quantity was 0.45 (95 % CI: 0.03 – 0.88; $I^2 = 74$ %; $p = 0.0003$; $Z = 2.10$, $p = 0.04$); and corneal staining 0.72 (95 % CI: 0.14 – 1.30; $I^2 = 85$ %; $p < 0.00001$; $Z = 2.43$, $p = 0.02$).

Conclusion: The current study shows that platelet-rich plasma is efficacious in managing dry eye disease, significantly reducing dry eye signs and symptoms. Such significant improvements could translate to improved quality of life.

1. Introduction

Dry eye disease, a multifactorial condition of the ocular surface, affects millions globally [1]. The public health significance and economic burden of dry eye disease have been well documented [2,3]. Risk factors for dry eye disease include age, gender, contact lens wear, systemic conditions such as diabetes, autoimmune disorders (e.g., Sjogren's syndrome), and environmental conditions such as low humidity [4]. Commonly reported dry eye symptoms are dryness, burning sensation, grittiness, sensitivity to light, and intermittent visual disturbance, leading to an overall reduction in the patient's quality of life [5–8].

Dry eye disease management options include ocular medications,

* Corresponding author.
E-mail addresses: pkakowua@central.uh.edu (P. Kwaku Akowuah), eowusu@uh.edu (E. Owusu), kbonsu@cougarnet.uh.edu (K. Bonsu), lucyakuaafriyie1@gmail.com (L.A.A. Karikari), kobiaacquah@yahoo.com (E. Kobia-Acquah).
[1] co-first authors.

https://doi.org/10.1016/j.clae.2023.102091
Received 6 August 2023; Received in revised form 20 October 2023; Accepted 4 November 2023
Available online 10 November 2023

environmental modifications, surgical options, and intense pulsated light therapy [9,10]. Mild dry eye disease is usually managed with artificial tears or ocular lubricants, which mainly reduce symptoms but fail to repair injured tissues. However, moderate and severe dry eye disease is typically unamendable to ocular lubricants and is treated with anti-inflammatory agents such as steroids. Topical steroids are associated with side effects such as increased intraocular pressure, cataracts, impaired wound healing, and elevated risk of ocular surface infection, making long-term use not viable [11]. Therefore, there is a need for therapies with better long-term use feasibility and fewer complications.

Alio and colleagues first described using platelet-rich plasma in treating ophthalmic conditions in 2007 [12]. Platelet-rich plasma has a high platelet concentration compared to peripheral blood [13]. Although similar in its preparation to platelet-rich plasma, plasma rich in growth factor is considered a subtype of platelet-rich plasma that is high in growth factors such as transforming growth factor-beta and platelet-derived growth factor, devoid of leukocytes and lacking proinflammatory activity [14]. Platelet-rich plasma has been explored in managing dry eye disease due to its rich concentration of anti-inflammatory agents and growth factors such as epidermal and platelet-derived growth factors, both beneficial for ocular surface repair. Platelet-rich plasma has successfully been used to treat ocular surface diseases, including dry eye disease, persistent epithelial defect, neurotrophic keratitis, etc. [15–19].

Although Bernabei et al. [20] and You et al. [21] reviewed studies on platelet-rich plasma for treating dry eye disease and other ocular surface conditions, none of the authors attempted to estimate this approach's beneficial and adverse effects using *meta*-analytic methods. The current study uses *meta*-analysis to summarize the benefits of platelet-rich plasma for treating dry eye disease and its adverse effects.

2. Methods

This review followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22] (Supplement 1). The study was registered on PROSPERO (ID: CRD42022347982).

2.1. Search strategy

Four online databases – PubMed, Google Scholar, Web of Science, and Scopus – were searched for literature on treating dry eye disease with platelet-rich plasma. The following keywords were used in the literature search: "dry eye disease" OR "Dry eye syndrome" OR "Dry eye" OR "DED" OR "ocular surface disease" OR "Ocular graft-versus-host disease" OR "Ocular GvHD" OR "Sjogren's syndrome" AND "platelet-rich plasma" OR "Blood platelets" OR "PRP." The complete search strategy used in PubMed is presented in Supplement 2. The last literature search was on December 20, 2022. Two reviewers independently performed the literature search.

2.2. Study selection and eligibility criteria

The inclusion criteria were:

1. Prospective comparative studies (randomized and non-randomized) using platelet-rich plasma to treat dry eye disease.
2. Platelet-rich plasma used as either mono or combination therapy.
3. Before-after studies, also known as pre and post studies, (i.e., studies without a control group) were only included if they reported the safety profile of platelet-rich plasma.
4. Subjective symptom scores and/or clinical signs before and after treatment or the change from baseline were reported.
5. Clinical outcomes were reported with mean or median.
6. A full-text study article must be available.

Studies were included regardless of platelet-rich plasma formulation methods, route of administration, or the control treatment used. Only published studies and/or abstracts with full text available were included. Before-after studies (prospective and retrospective) were only used to analyze platelet-rich plasma treatment's adverse effects (safety). For the assessment of clinical outcomes, only prospective comparative studies were used. Full-text articles of studies that passed the initial screening were obtained and screened for eligibility by two reviewers. Discussions with a third reviewer resolved article eligibility issues.

Primary outcome

1. Improvement in dry eye symptoms post-platelet-rich plasma treatment.
2. Occurrence of adverse effects

Secondary outcomes
Improvement in:

1. Tear quality post-platelet-rich plasma treatment
2. Tear quantity post-platelet-rich plasma treatment
3. Corneal staining post-platelet-rich plasma treatment

2.3. Data extraction and study appraisal

The following information was extracted from each study: authors' names, study location, study design, sample size, age, gender, dose/frequency, route of administration, control treatment, follow-up, clinical outcomes, and adverse effects.

The following tools were used to assess the quality of included studies:

1. Before-After studies - NIH (National Institutes of Health) quality assessment tool for before-after studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).
2. Randomized controlled studies - Cochrane risk of bias tool (RoB2)
3. Non-randomized controlled studies - Methodological index for non-randomized studies (MINORS)

The result of quality assessments is presented in Supplement 3. Two reviewers independently conducted data extraction and study quality assessments; discussions with a third reviewer resolved disagreements.

2.4. Data synthesis and analysis

Statistical analysis was performed using Review Manager (version 5.4). Clinical outcomes were assessed using standardized mean difference (SMD) with a 95 % confidence interval. The occurrence of adverse effects was evaluated using proportion with a 95 % confidence interval. For studies reporting results with median and interquartile range or range, the mean and standard deviation were estimated using the methods described by Wan et al.[23]. For studies that did not report the standard deviation for mean change from baseline, the methods described in the Cochrane Handbook for Systematic Reviews of Interventions were used to compute the standard deviation (https://training.cochrane.org/handbook). When calculating the standard deviation from p-values, a conservative approach was adopted if a study reported the level of significance instead of the exact p-value. For example, for a significance level of $p < 0.05$, a p-value of 0.05 was used in the calculation. The degree of inconsistency (I^2) was used to assess heterogeneity between studies. Significant heterogeneity was considered as $I^2 \geq 50$ %[24]. A random-effects model was used for analysis when heterogeneity was significant, and a fixed-effect model when heterogeneity was non-significant. Sub-group analysis was conducted to explore sources of heterogeneity; factors considered included study design, control treatment used, and route of administration. Forest plots were used for the graphical presentation of findings. For all statistical

analyses, a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Literature search

1002 records were obtained from the database search. 554 duplicates were identified and removed. 19 studies were included in the systematic review and *meta*-analysis. Fig. 1 shows the steps in screening for eligible studies.

3.2. Study characteristics

Table 1 summarizes the characteristics of the studies included in the *meta*-analysis. Ten (10) studies were comparative studies: 6 randomized [25–30] and 4 non-randomized studies [19,31–33]. In addition, 3 studies were prospective pre-post studies [34–36], and 6 were retrospective pre-post studies [37–42].

3.3. Meta-analysis

3.3.1. Occurrence of adverse effects

Nine studies reported on the safety profile. The overall pooled rate of adverse effects was 2.6 % (95 % CI: 0.5 – 4.7). The common adverse effects reported were itchy eye, irritation, and dizziness.

For traditional platelet-rich plasma (5 studies), the rate of occurrence of adverse events was 2.5 % (95 % CI: −0.6 – 5.6), while for plasma rich in growth factor (4 studies), the rate of occurrence of adverse events was 4.1 % (95 % CI: −0.6 – 8.5).

3.3.2. Clinical outcomes

The pooled standardized mean difference for dry eye symptoms was 0.81 (95 % CI: 0.25 – 1.37; $I^2 = 82$ %; $p < 0.00001$). The overall effect size was statistically significant ($Z = 2.84$, $p = 0.004$). Fig. 2 shows the forest plot for the symptom scores for comparative studies.

The pooled standardized mean difference for tear quality was 0.44 (95 % CI: 0.06 – 0.81; $I^2 = 67$ %; $p = 0.003$), with a statistically significant overall effect size ($Z = 2.26$, $p = 0.02$) (Fig. 3A). Similarly, the pooled standardized mean difference for tear quantity was 0.45 (95 % CI: 0.03 – 0.88; $I^2 = 74$ %; $p = 0.0003$), also showing statistically significant overall effect size ($Z = 2.10$, $p = 0.04$) (Fig. 3B).

Fig. 3C shows the forest plot for the corneal staining. The pooled standardized mean difference was 0.72 (95 % CI: 0.14 – 1.30; $I^2 = 85$ %; $p < 0.00001$). The overall effect size was statistically significant ($Z = 2.43$, $p = 0.02$).

3.4. Subgroup analysis

3.4.1. Symptoms

The standardized mean difference for randomized and non-randomized controlled studies were 0.59 (95 % CI: −0.45 – 1.63; $Z = 1.11$, $p = 0.27$; $I^2 = 91$ %) and 0.99 (95 % CI: 0.52 – 1.46; $Z = 4.16$, $p < 0.0001$; $I^2 = 38$ %), respectively. No significant difference in effect size was observed between randomized and non-randomized controlled studies ($p = 0.73$).

Studies using autologous serum as a control treatment had a standardized mean difference of 0.16 (95 % CI: −2.04 – 2.36; $Z = 0.14$, $p = 0.89$; $I^2 = 91$ %, $p = 0.0009$), while studies using artificial tears/hyaluronan had a standardized mean difference of 0.99 (95 % CI: 0.45 – 1.52; $Z = 3.61$, $p = 0.0003$; $I^2 = 78$ %, $p = 0.0003$). No significant difference was found between the studies using different control treatments ($p = 0.47$).

The standardized mean difference for eye drop administration was 0.95 (95 % CI: 0.41 – 1.49; $Z = 3.45$, $p = 0.0006$; $I^2 = 77$ %, $p = 0.0007$), while for lacrimal region injection administration, it was 0.26 (95 % CI: −2.10 – 2.62; $Z = 0.22$, $p = 0.83$; $I^2 = 94$ %, $p < 0.0001$). There was no significant difference in the effect size between the eye drop and lacrimal region injection routes of administration ($p = 0.58$).

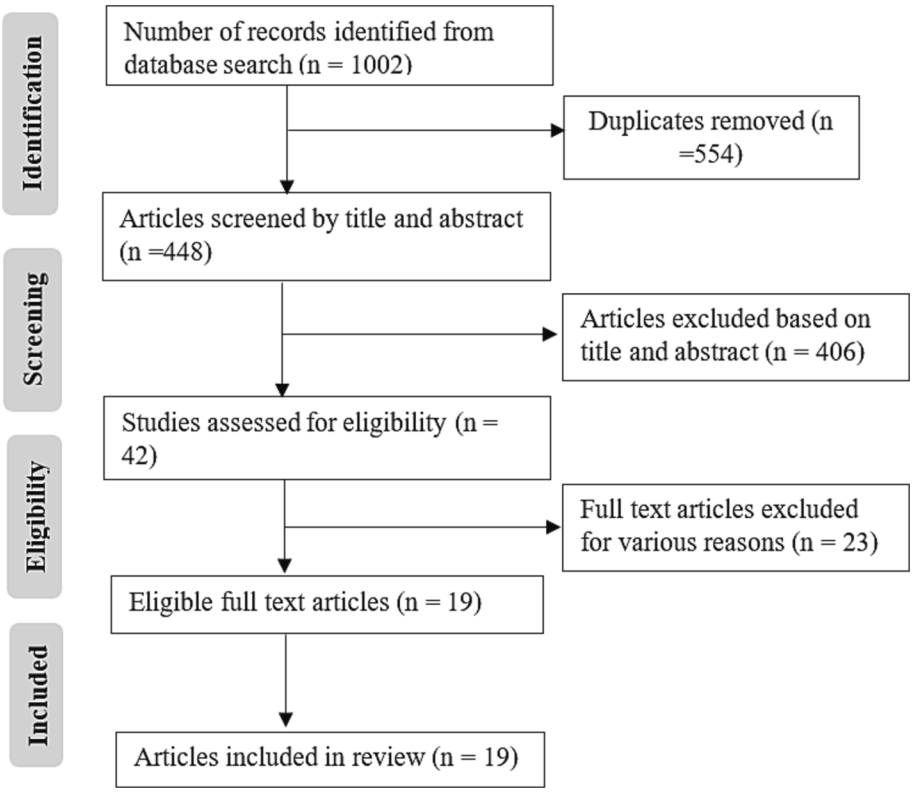

Fig. 1. PRISMA flowchart of steps in identifying studies. 1002 records were identified from the online literature search. 20 articles were included in the study.

Table 1
Characteristics of studies included in the systematic review and *meta*-analysis.

a. Comparative (controlled) clinical studies.

Authors	Location	Study design	Sample size		Age (mean ± SD)		Condition	Treatment		Dose/Frequency		Follow-up	
			Treatment (M/F)	Control (M/F)	Treatment	Control		Treatment	Control	Treatment	Control	Treatment	Control
Rawat et al., 2022[31]	India	Non-randomized controlled study	11/20	12/18	52.8 ± 12.8	55.5 ± 13.4	Dry eye disease	Autologous platelet-rich plasma	Carboxymethyl cellulose	1 drop 4–6X daily	1 drop 4–6X daily	3 months	3 months
Avila et al., 2018 [29]	Columbia	Randomized controlled study	1/14	1/14	59.2 ± 3.4	52.7 ± 3.5	Dry eye disease secondary to Sjogren's syndrome	Autologous platelet-rich plasma	Hyaluronic acid	1 ml injection in the lacrimal region per month	n.s	3 months	3 months
Fea et al., 2016 [19]	Italy	Non-randomized controlled study	1/19	0/10	60.4 ± 11.6	59.5 ± 13.3	Dry eye disease secondary to Sjogren's syndrome	Autologous platelet-rich plasma	Hyaluronic acid	1 drop 4X daily	1 drop 4X daily	3 months	3 months
Garcia-Conca et al., 2019 [25]	Spain	Randomized controlled study	44	39	62.1 ± 11.2	66.2 ± 11.0	Hyposecretory Dry eye disease	Autologous platelet-rich plasma	Sodium hyaluronate	1 drop 6X daily	1 drop 6X daily	1 month	1 month
Elessawy et al., 2021[28]	Egypt	Randomized controlled study	4/16	6/14	54 ± 10	51 ± 6	Severe dry eye disease	Autologous platelet-rich plasma	Artificial tears	1 ml injection in the lacrimal region per month	n.s	3 months	3 months
Mohammad et al., 2022 [30]	Egypt	Randomized controlled study	9/21	8/22	50.5 ± 12.8	46.3 ± 12.9	Severe dry eye disease	Autologous platelet-rich plasma	Autologous serum	1 drop 6X daily	1 drop 6X daily	3 months	3 months
Wróbel-Dudzińska et al., 2023 [33]	Poland	Non-randomized controlled study	0/11	0/11	62.2 ± 8.3	62.9 ± 10.9	Dry eye disease secondary to Sjogren's syndrome	Autologous platelet-rich plasma	Autologous serum	1 drop 5X daily	1 drop 5X daily	3 months	3 months
Wahdan, 2019 [32]	Egypt	Non-randomized controlled study	15	15	n.s	n.s	Dry eye disease	Autologous platelet-rich plasma	Sodium hyaluronate	1 drop 6X daily	1 drop 6X daily	1.5 months	1.5 months
Allam, 2021[26]	Egypt	Randomized controlled study	10	10	n.s.	n.s.	Severe dry eye disease	Autologous platelet-rich plasma	Autologous serum	1 ml injection in the lacrimal region per month	1 drop 5X daily	3 months	3 months
Emam et al., 2021[27]	Egypt	Randomized controlled study	13/18	11/20	n.s.	n.s.	Moderate to severe dry eye disease	Autologous platelet-rich plasma	Artificial tears	1 drop 4X daily	1 drop 4X daily	1.5 months	1.5 months

b. Non-comparative (pre-post) clinical studies

Authors	Location	Study type	Study design	Sample size	Male/ Female	Age (mean ± SD)	Condition	Dose/Frequency	Follow-up
Alio et al., 2017[34]	Spain	Prospective	Cohort	232	n.s.	n.s.	Evaporative dry eye disease	1 drop per eye, 6X daily	6 weeks or more
Pezzotta et al., 2017[35]	Italy	Prospective	Cohort	31	21/10	47 (7.7)	Dry eye disease secondary to ocular Graft-versus-Host Disease	4X daily	36 months
Avila et al., 2014[36]	Columbia	Prospective	Case series	4	n.s.	n.s.	Severe dry eye disease	1 ml injection in lacrimal region per month	3 months
Sanchez-Avila et al., 2017 [38]	Spain	Retrospective	Case series	26	0/26	59.9 (14.9)	Dry eye disease secondary to Sjogren's syndrome	4X daily	3 months
Sanchez-Avila et al., 2017 [40]	Spain	Retrospective	Cohort	21	6/15	53.5 (14.7)	Dry eye disease secondary to Laser-assisted in situ keratomileusis	4X daily	1.5 months
Merayo-Lloves, 2016[37]	Spain	Retrospective	Cohort	83	17/66	58.8 (16.87)	Evaporative dry eye disease	4X daily	6 months
Sanchez-Avila et al., 2020 [39]	Spain	Retrospective	Case series	12	9/3	54.1 (10.8)	Dry eye disease secondary to ocular Graft-versus-Host Disease	4X daily	3 months
Sanchez-Avila et al., 2018 [42]	Spain	Retrospective	Case series	31	15/16	58.58 (17.71)	Dry eye disease secondary to neurotrophic keratitis	4X daily for 6, or 12 weeks	3 months
Murtaza et al., 2022[41]	Canada	Retrospective	Case series	10	5/5	n.s	Evaporative dry eye disease	6X daily for 4 weeks	1 month

SD – Standard deviation; n.s - Not stated

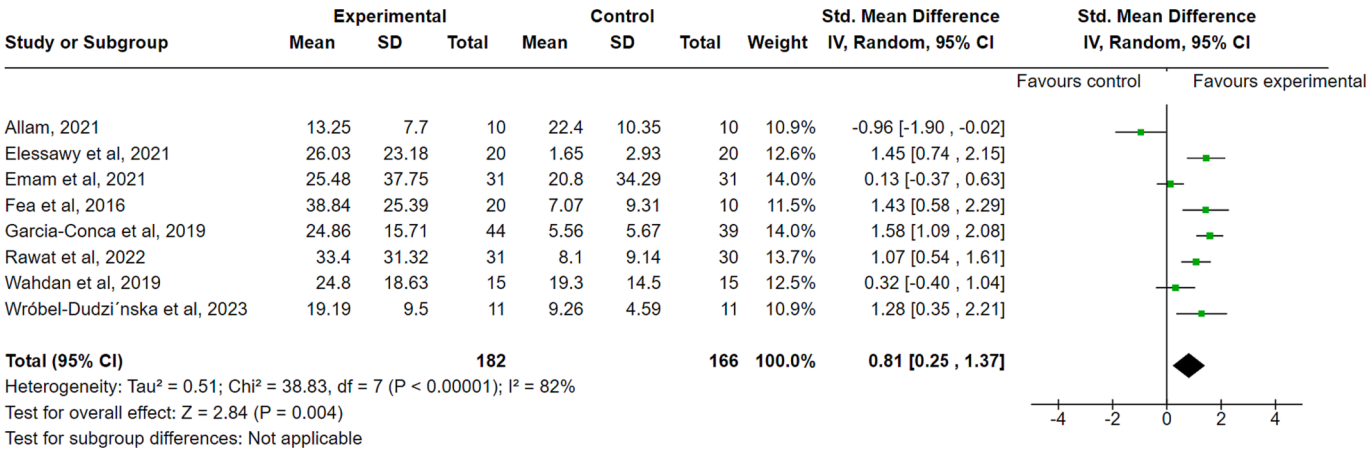

Fig. 2. Forest plot for the change of dry eye symptom score following platelet-rich plasma treatment compared to control treatment. The pooled SMD was 0.81 (95 % CI: 0.25 – 1.37). Experimental – Platelet-rich plasma; Control – autologous serum/hyaluronan/artificial tears; SD – standard deviation; black diamond represents pooled estimates; the size of the green square represents the weight of each study. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4.2. Tear quality

The standardized mean difference for randomized and non-randomized controlled studies was 0.13 (95 % CI: −0.11 – 0.37; Z = 1.07, p = 0.29; I^2 = 0 %, p = 0.58) and 1.15 (95 % CI: 0.75 – 1.56; Z = 5.62, p < 0.0001; I^2 = 0 %, p = 0.84), respectively, indicating a significant difference in effect size between the two study types (p < 0.0001).

Studies using autologous serum as a control treatment had a standardized mean difference of 0.31 (95 % CI: −0.59 – 1.22; Z = 0.68, p = 0.50; I^2 = 76 %, p = 0.02), while those using artificial tears/hyaluronan had a standardized mean difference of 0.50 (95 % CI: 0.06 – 0.94; Z = 2.24, p = 0.02; I^2 = 68 %, p = 0.02). No significant difference was observed between the studies using different control treatments (p = 0.72).

The standardized mean difference for eye drop administration was 0.62 (95 % CI: 0.22 – 1.02; Z = 3.03, p = 0.002; I^2 = 65 %, p = 0.01), whereas, for lacrimal region injection administration, it was −0.20 (95 % CI: −0.71 – 0.31; Z = 0.76, p = 0.44; I^2 = 0 %, p = 0.40). A significant difference in effect size was found between the eye drop and lacrimal region injection routes of administration (p = 0.01).

3.4.3. Tear quantity

The standardized mean difference for randomized and non-randomized controlled studies were 0.53 (95 % CI: 0.21 – 0.85; Z = 3.25, p = 0.001; I^2 = 36 %, p = 0.18) and 0.43 (95 % CI: −0.77 – 1.63; Z = 0.70, p = 0.48; I^2 = 88 %, p = 0.0002), respectively. No significant difference in the effect size between randomized and non-randomized controlled studies was observed (p = 0.88).

The standardized mean difference for studies using autologous serum as control treatment was 0.52 (95 % CI: −0.03 – 1.08; Z = 1.84, p = 0.07; I^2 = 40 %, p = 0.19); artificial tears/hyaluronan was 0.42 (95 % CI: −0.18 – 1.03; Z = 1.38, p = 0.17; I^2 = 83 %, p = 0.0001). There was no significant difference between studies using the various control groups (p = 0.81).

The standardized mean difference for eye drop administration was 0.44 (95 % CI: −0.06 – 0.95; Z = 1.72, p = 0.09; I^2 = 79 %, p = 0.0003), and for lacrimal region injection administration was 0.49 (95 % CI: −0.48 – 1.46; Z = 0.99, p = 0.32; I^2 = 68 %, p = 0.60). No significant difference in the effect size between eye drop and lacrimal area injection route of administration was observed (p = 0.93).

3.4.4. Corneal staining

The standardized mean difference for randomized controlled studies was 0.83 (95 % CI: 0.06 – 1.60; Z = 2.11, p = 0.04; I2 = 88 %, p < 0.00001) and for non-randomized controlled studies was 0.44 (95 % CI: −0.46 – 1.34; Z = 0.95, p = 0.34; I2 = 76 %, p = 0.04). No significant difference in the effect size between randomized and non-randomized controlled studies was observed (p = 0.52).

The standardized mean difference for studies using autologous serum as control treatment was 0.46 (95 % CI: [-0.76 – 1.68; Z = 0.74, p = 0.46; I^2 = 82 %, p = 0.02); artificial tears/hyaluronan was 0.81 (95 % CI: 0.06 – 1.55; Z = 2.13, p = 0.03; I2 = 88 %, p < 0.00001); and artificial tears was 0.66 (95 % CI: 0.07 – 1.25; Z = 2.18, p = 0.03; I^2 = 70 %, p = 0.04). There was no significant difference between studies using the various control groups (p = 0.90).

The standardized mean difference for eye drop administration was 0.80 (95 % CI: 0.09 – 1.52; Z = 2.20, p = 0.03; I^2 = 88 %, p < 0.00001) and for lacrimal region injection administration was 0.46 (95 % CI: −0.80 – 1.73; Z = 0.72, p = 0.47; I^2 = 81 %, p = 0.02). No significant difference in the effect size between eye drop and lacrimal area injection route of administration was observed (p = 0.65).

Table 2 summarizes the results of the subgroup analysis. The forest plots for the subgroup analysis are presented in Supplement 4–7.

4. Discussion

Management of dry eye disease has shifted from artificial tears to options such as anti-inflammatory and immune-modulatory agents and biological tear substitutes [43] in recent years, following the recognition of inflammation and hyperosmolarity as the underlying cause of dry eye disease [1]. Biological tear substitutes such as autologous serum and platelet-rich plasma preparations share similar characteristics (including pH, nutritional content, and growth factors) to human tears [43]. Platelet-rich plasma preparations are useful in managing ocular surface defects due to their high concentration of growth factors and anti-inflammatory agents. Compared to autologous serum, platelet preparations have more essential growth factors and cell adhesion molecules necessary for ocular surface healing [44].

The current systematic review and *meta*-analysis revealed a significant improvement in subjective dry eye symptoms with platelet-rich plasma compared to artificial tears/hyaluronan control treatments. Conversely, there were no differences in improvement in dry eye symptoms between platelet-rich plasma and autologous serum, suggesting similar effects for both treatments on dry eye symptom relief. Most patients with dry eye disease experience ocular surface symptoms that affect their quality of life; hence, treating dry eye symptoms is essential to patient functionality and rehabilitation. Artificial tears relieve dry eye symptoms by lubricating the ocular surface, treating the

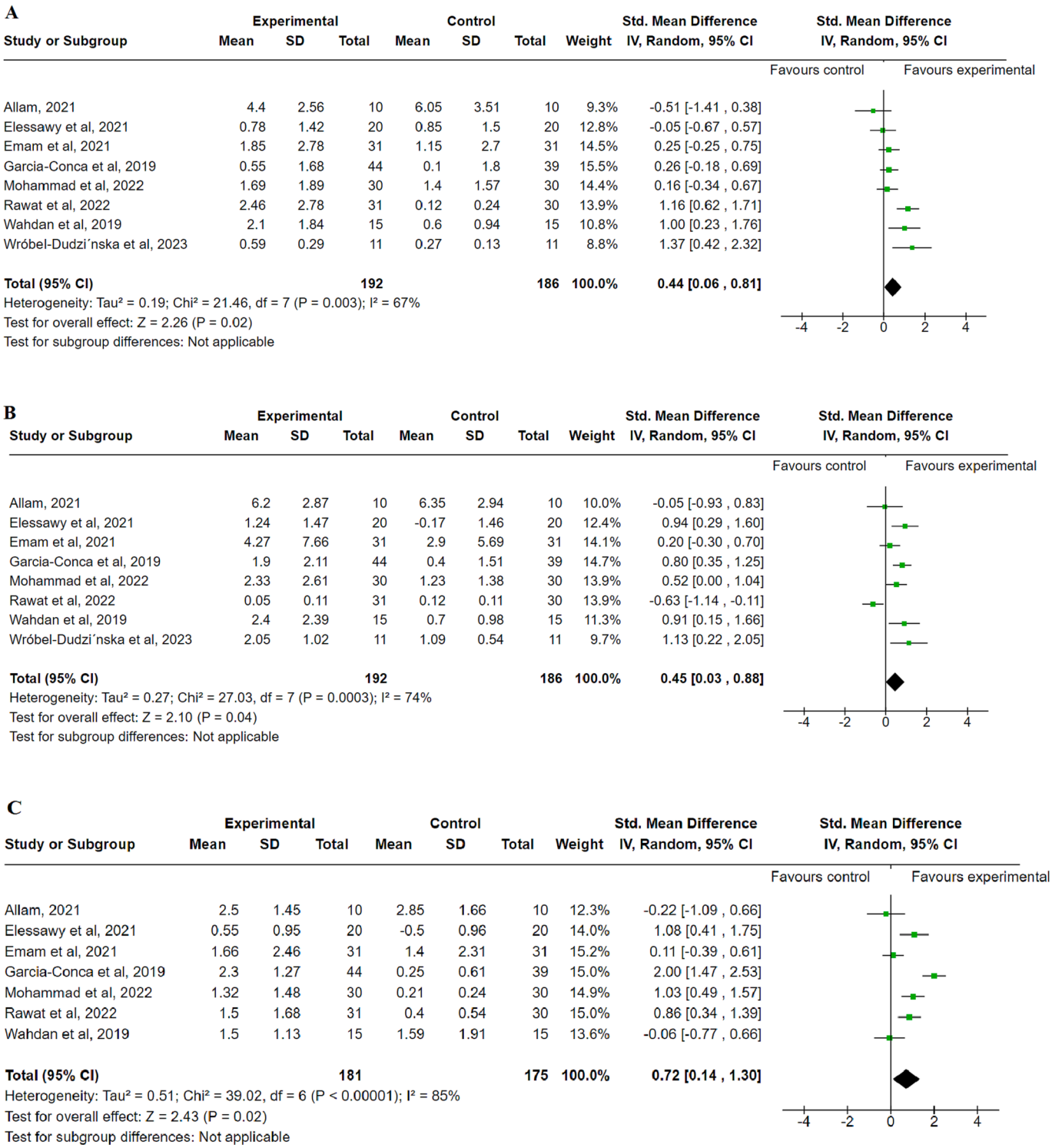

Fig. 3. Forest plots for the change in tear quality (A), tear quantity (B) and corneal staining (C) scores following platelet-rich plasma treatment compared to control treatment. The pooled standardized mean difference for tear quality was 0.44 (95 % CI: 0.06 – 0.81); tear quantity was 0.45 (95 % CI: 0.03 – 0.88); and corneal staining was 0.72 (95 % CI: 0.14 – 1.30). Experimental – Platelet-rich plasma; Control – autologous serum/hyaluronan/artificial tears; SD – standard deviation; black diamond represents pooled estimates; green square size represents each study's weight. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

symptoms but not the underlying causes. Other disadvantages of artificial tears include the need for frequent drop application and lower efficacy after long-standing treatment, with some preservative-containing artificial tears paradoxically exacerbating dry eye symptoms [34]. The Dry Eye Workshop II (DEWS II) report, therefore, recommends autologous serum and platelet-rich plasma in step 3 of dry eye disease management [43]. Both autologous serum and platelet-rich plasma contain growth factors that improve ocular surface health, facilitate wound healing, and lubricate the ocular surface. However, platelet-rich plasma is richer in growth factors than autologous serum due to the loss of platelets during autologous serum preparation and dilution. Despite autologous serum containing pro-inflammatory enzymes such as matrix

Table 2
Summary of subgroup analysis.

Subgroup		Symptoms		Tear quality		Tear quantity		Corneal staining	
		N	Effect size	N	Effect size	N	Effect size	N	Effect size
Study design	Randomized	4	0.59 (95 %CI: −0.45 – 1.63)	5	0.13 (95 % CI: −0.11 – 0.37)	5	0.53 (95 % CI: 0.21 – 0.85)	5	0.83 (95 % CI: 0.06 – 1.60)
	Non-randomized	4	0.99 (95 % CI: 0.52 – 1.46)	3	1.15 (95 % CI: 0.75 – 1.56)	3	0.43 (95 % CI: −0.77 – 1.63)	2	0.44 (95 % CI: −0.46 – 1.34)
	Subgroup difference	p = 0.73		p < 0.0001		p = 0.88		p = 0.52	
Control treatment	Autologous serum	2	0.16 (95 % CI: −2.04 – 2.36)	3	0.31 (95 % CI: −0.59 – 1.22)	3	0.52 (95 % CI: −0.03 – 1.08)	2	0.46 (95 % CI: [-0.76 – 1.68)
	Artificial tears/ Hyaluronan	6	1.13 (95 % CI: 0.33 – 1.93)	5	0.50 (95 % CI: 0.06 – 0.94)	5	0.42 (95 % CI: −0.18 – 1.03)	5	0.81 (95 % CI: 0.06 – 1.55)
	Subgroup difference	p = 0.47		p = 0.72		p = 0.81		p = 0.63	
Route of administration	Eye drops	6	0.95 (95 % CI: 0.41 – 1.49)	6	0.62 (95 % CI: 0.22 – 1.02)	6	0.44 (95 % CI: −0.06 – 0.95)	5	0.80 (95 % CI: 0.09 – 1.52)
	Lacrimal region injection	2	0.26 (95 % CI: −2.10 – 2.62)	2	−0.20 (95 % CI: −0.71 – 0.31)	2	0.49 (95 % CI: −0.48 – 1.46)	2	0.46 (95 % CI: −0.80 – 1.73
Subgroup difference		p = 0.58		p = 0.01		p = 0.93		p = 0.65	

N - number of studies.

metalloproteinases [45], this fundamental difference potentially decreases the efficacy of autologous serum compared to platelet-rich plasma [46]. Aside from being a substitute for artificial tears and sharing similar characteristics to human tears, platelet-rich plasma is preservative-free and has a high content of epithelial growth factors, insulin-like growth factors, vitamin A [47], and anti-inflammatory properties [15].

The current study showed significant improvements in tear quality and production in dry eye disease following platelet-rich plasma treatment. The improvement of tear quantity score suggests tear/lacrimal volume increase either due to suppression of the inflammation of the lacrimal functional unit or stimulation of the lacrimal system, while improvement in tear quality suggests increased stability of the lacrimal film that may support improved mucin secretion by the conjunctival goblet cells and/or the lacrimal gland. Improvement in tear quality may also suggest improved quality of the lipid layer of the tear film.

Corneal staining is useful for assessing disease severity and monitoring response to treatment of dry eye disease. In addition, the morphological pattern and topographical distribution of corneal staining help determine the underlying etiology of dry eye [48]. Corneal stains, therefore, are an important dry eye disease diagnostic test recommended in TFOS DEWS II guidelines [49]. The current study observed a significant improvement in corneal staining following platelet-rich plasma treatment, potentially due to tissue regeneration initiated by the growth factors in platelet-rich plasma.

For all ocular surface parameters assessed, using lacrimal injection as the route of administration produced no significant beneficial effect. However, administering platelet-rich plasma as eye drops produced clinically significant improvements in dry eye symptoms, tear quality, tear quantity, and corneal staining. Injection is a common drug administration approach when specific tissue regeneration is needed. Platelet-rich plasma is employed for tissue regeneration as it creates a local environment rich in growth factors and other cytokines, influencing the migration and proliferation of several cell types [50]. Lacrimal gland injection of platelet-rich plasma aims to stimulate the lacrimal gland and would be most effective if a compromised lacrimal gland is the major etiology of dry eye disease [51]. However, lacrimal gland injection may not be suitable for administering platelet-rich plasma and other treatments if the etiology of the dry eye disease is not lacrimal gland related, e.g., meibomian gland dysfunction-related dry eye disease or goblet cells-related (mucin-deficiency) dry eye disease.

Despite the numerous benefits of platelet-rich plasma in managing dry eye disease, it is essential to note that some studies have reported some adverse effects. Side effects attributed to the use of platelet-rich plasma include itching [37,42] and dizziness [37], conjunctivitis [19], eye pain [18], and irritation [38]. A primary safety consideration for blood-based eye drops, such as platelet-rich plasma and autologous serum, is the risk of microbial contamination during preparation and storage. There is a requirement for strict adherence to sterile procedures in preparing and storing these eye drops, necessitating proper patient care and use instructions to minimize contamination.

Using platelet-rich plasma for dry eye disease treatment presents several advantages, including the autologous nature, ease of preparation, and cost-effectiveness. Platelet-rich plasma contains platelets, growth factors, and cytokines; these facilitate corneal epithelial cell proliferation, migration, and differentiation, thus helping to maintain optimal ocular surface conditions [52,53]. Moreover, autologous platelet-rich plasma has been used successfully in other ocular surface disorders such as post-LASIK ocular surface disorder, persistent epithelial defects, alkali burn, and corneal surface reconstructions [15,54–56].

A limitation in this systematic review and *meta*-analysis was the observed heterogeneity, which may have been due to the variation in the methods of the studies included, such as the use of an invasive method (fluorescein dye) to assess the tear quality, which can destabilize the tear film [49]. Similarly, the use of Schirmer's strips without anesthesia to assess tear production, though standardized, also has limitations, potentially resulting in variability of the results obtained [49]. A key strength of the current *meta*-analysis is the inclusion of studies investigating different forms of dry eye disease, including ocular GVHD, Sjögren's syndrome, etc., and a diverse population of subjects. Improving subjective dry eye symptoms, tear production, and quality in the different dry eye disease types studied suggests that platelet-rich plasma can effectively manage ocular surface disease. Since TFOS recommends autologous platelet-rich plasma drops as a step 3 management strategy for dry eye disease [43], the results from this *meta*-analysis bear direct clinical relevance and impact on the eye care practitioner.

5. Conclusion

The current study shows that platelet-rich plasma is efficacious in managing dry eye disease, significantly reducing dry eye signs and symptoms with platelet-rich plasma treatment. Such significant improvements could translate to improved quality of life.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clae.2023.102091.

References

[1] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf 2017;15:276–83. https://doi.org/10.1016/j.jtos.2017.05.008.

[2] McDonald M, Patel DA, Keith MS, Snedecor SJ. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: a systematic literature review. Ocular Surface 2016;14:144–67. https://doi.org/10.1016/j.jtos.2015.11.002.

[3] Yamada M, Mizuno Y, Shigeyasu C. Impact of dry eye on work productivity. ClinicoEconomics and Outcomes Research 2012;4:307–12. https://doi.org/10.2147/CEOR.S36352.

[4] Messmer EM. Pathophysiology, diagnosis and treatment of dry eye. Dtsch Arztebl Int 2015;112:71–81. https://doi.org/10.3238/arztebl.2015.0071.

[5] Nichols KK. Patient-reported symptoms in dry eye disease. Ocul Surf 2006;4:137–45. https://doi.org/10.1016/S1542-0124(12)70040-X.

[6] Barabino S, Labetoulle M, Rolando M, Messmer EM. Understanding symptoms and quality of life in patients with dry eye syndrome. Ocul Surf 2016;14:365–76. https://doi.org/10.1016/j.jtos.2016.04.005.

[7] Gomes JAP, Santo RM. The impact of dry eye disease treatment on patient satisfaction and quality of life: a review. Ocul Surf 2019;17:9–19. https://doi.org/10.1016/j.jtos.2018.11.003.

[8] Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol 2007;143:409–15. https://doi.org/10.1016/j.ajo.2006.11.060.

[9] Buckley RJ. Assessment and management of dry eye disease. Eye 2018;32:200–3.

[10] Rouen PA, White ML. Dry eye disease: prevalence, assessment, and management. Home Healthc Now 2018;36:74–83.

[11] McGhee CNJ, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf 2002;25:33–55. https://doi.org/10.2165/00002018-200225010-00004.

[12] Alio JL, Abad M, Artola A, Rodriguez-Prats JL, Pastor S, Ruiz-Colecha J. Use of autologous platelet-rich plasma in the treatment of dormant corneal ulcers. Ophthalmology 2007;114. https://doi.org/10.1016/J.OPHTHA.2006.10.044.

[13] Anitua E, de la Sen-Corcuera B, Orive G, Sánchez-Ávila RM, Heredia P, Muruzabal F, et al. Progress in the use of plasma rich in growth factors in ophthalmology: from ocular surface to ocular fundus. Expert Opin Biol Ther 2022;22:31–45. https://doi.org/10.1080/14712598.2021.1945030.

[14] Solakoglu Ö, Heydecke G, Amiri N, Anitua E. The use of plasma rich in growth factors (PRGF) in guided tissue regeneration and guided bone regeneration. a review of histological, immunohistochemical, histomorphometrical, radiological and clinical results in humans. Ann Anat 2020;231. https://doi.org/10.1016/J.AANAT.2020.151528.

[15] Alio JL, Rodriguez AE, Abdelghany AA, Oliveira RF. Autologous platelet-rich plasma eye drops for the treatment of post-LASIK chronic ocular surface syndrome. J Ophthalmol 2017;2017:2457620. https://doi.org/10.1155/2017/2457620.

[16] Alio JL, Colecha JR, Pastor S, Rodriguez A, Artola A. Symptomatic dry eye treatment with autologous platelet-rich plasma. Ophthalmic Res 2007;39:124–9.

[17] Ribeiro MVMR, Barbosa FT, Ribeiro LEF, Lacet CMC, de Lyra JM, AG, Guedes V de L,, et al. Platelet-rich plasma in diabetic dry eye disease. Rev Bras Oftalmol 2016;75:308–13. https://doi.org/10.5935/0034-7280.20160061.

[18] Zallio F, Mazzucco L, Monaco F, Astori MR, Passera R, Drago G, et al. A single-center pilot prospective study of topical application of platelet-derived eye drops for patients with ocular chronic graft-versus-host disease. Biol Blood Marrow Transplant 2016;22:1664–70. https://doi.org/10.1016/J.BBMT.2016.05.023.

[19] Fea AM, Aragno V, Testa V, Machetta F, Parisi S, D'antico S, et al. The effect of autologous platelet lysate eye drops: an in vivo confocal microscopy study. Biomed Res Int 2016;2016. https://doi.org/10.1155/2016/8406832.

[20] Bernabei F, Roda M, Buzzi M, Pellegrini M, Giannaccare G, Versura P. Blood-based treatments for severe dry eye disease: the need of a consensus. J Clin Med 2019;8. https://doi.org/10.3390/JCM8091478.

[21] You J, Hodge C, Hoque M, Petsoglou C, Sutton G. Human platelets and derived products in treating ocular surface diseases – a systematic review. Clin Ophthalmol 2020;14:3195. https://doi.org/10.2147/OPTH.S265701.

[22] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;7:e1000097. https://doi.org/10.1371/journal.pmed.1000097.

[23] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014:14. https://doi.org/10.1186/1471-2288-14-135.

[24] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.

[25] García-Conca V, Abad-Collado M, Hueso-Abancens JR, Mengual-Verdú E, Piñero DP, Aguirre-Balsalobre F, et al. Efficacy and safety of treatment of hyposecretory dry eye with platelet-rich plasma. Acta Ophthalmol 2019;97:e170–8. https://doi.org/10.1111/AOS.13907.

[26] Allam IY. Autologous serum eye drops versus lacrimal gland injection of platelet-rich plasma for severe dry eye. Delta Journal of Ophthalmology 2021;22:251. https://doi.org/10.4103/DJO.DJO_16_21.

[27] Emam DHF, El Mashad GY, Alkawas AA, El Deen SMS. Evaluating the role of autologous platelet-rich-plasma in the treatment of dry eye disease. Egypt J Hosp Med 2021;84:2065–70. https://doi.org/10.21608/EJHM.2021.180354.

[28] Elessawy KB, Araissi AB, Nasr HE, Abdelbaky SH. Assessment of the efficacy of platelet-rich plasma injections in the management of severe dry eye. Journal of the Egyptian Ophthalmological Society 2021;114:63. https://doi.org/10.4103/EJOS.EJOS_26_21.

[29] Avila MY, Igua AM, Mora AM. Randomised, prospective clinical trial of platelet-rich plasma injection in the management of severe dry eye. Br J Ophthalmol 2018;103:648–53. https://doi.org/10.1136/BJOPHTHALMOL-2018-312072.

[30] Mohammad EA, Lamie NM, Ismail AN, Mansour MN. Autologous Platelet Rich Plasma versus Autologous Serum Eye Drops in Treatment of Severe Dry Eye Disease. International Journal of Medical Arts 2022;4:2542–9. https://doi.org/10.21608/IJMA.2022.152958.1490.

[31] Rawat P, Agrawal R, Bhaisare V, Walia S, Kori N, Gupta R. Autologous platelet-rich plasma eye drop versus artificial tear eye drop for symptomatic dry eye disease: a prospective comparative interventional study. Indian J Ophthalmol 2022;70:1549–53. https://doi.org/10.4103/IJO.IJO_2595_21.

[32] Wahdan MM, Ibrahim MM-A, Elaraby MFA. Assessment of autologous (platelet-rich-plasma) as a monotherapy for treatment of dry eye disease. Egypt J Hosp Med 2019;76:4092–8. https://doi.org/10.21608/EJHM.2019.42651.

[33] Wróbel-Dudzińska D, Przekora A, Kazimierczak P, Ćwiklińska-Haszcz A, Kosior-Jarecka E, Żarnowski T. The comparison between the composition of 100% autologous serum and 100% platelet-rich plasma eye drops and their impact on the treatment effectiveness of dry eye disease in primary sjogren syndrome. J Clin Med 2023;12:3126. https://doi.org/10.3390/JCM12093126.

[34] Alio JL, Rodriguez AE, Ferreira-Oliveira R, Wróbel-Dudzińska D, Abdelghany AA. Treatment of dry eye disease with autologous platelet-rich plasma: a prospective, interventional. Non-Randomized Study Ophthalmol Ther 2017;6:285–93. https://doi.org/10.1007/S40123-017-0100-Z/TABLES/2.

[35] Pezzotta S, Del Fante C, Scudeller L, Rossi GC, Perotti C, Bianchi PE, et al. Long-term safety and efficacy of autologous platelet lysate drops for treatment of ocular GvHD. Bone Marrow Transplant 2017;52:101–6. https://doi.org/10.1038/BMT.2016.221.

[36] Avila MY. Restoration of human lacrimal function following platelet-rich plasma injection. Cornea 2014;33:18–21. https://doi.org/10.1097/ICO.0000000000000016.

[37] Merayo-Lloves J, Sanchez-Avila RM, Riestra AC, Anitua E, Begoña L, Orive G, et al. Safety and efficacy of autologous plasma rich in growth factors eye drops for the treatment of evaporative dry eye. Ophthalmic Res 2016;56:68–73. https://doi.org/10.1159/000444496.

[38] Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Anitua E, Muruzabal F, Orive G, et al. The effect of immunologically safe plasma rich in growth factor eye drops in patients with sjögren syndrome. J Ocul Pharmacol Ther 2017;33:391–9. https://doi.org/10.1089/JOP.2016.0166.

[39] Sanchez-Avila RM, Merayo-Lloves J, Muruzabal F, Orive G, Anitua E. Plasma rich in growth factors for the treatment of dry eye from patients with graft versus host diseases. Eur J Ophthalmol 2020;30:94–103. https://doi.org/10.1177/1120672118818943.

[40] Sanchez-Avila RM, Merayo-Lloves J, Fernandez ML, Rodriguez-Gutierrez LA, Jurado N, Muruzabal F, et al. plasma rich in growth factors for the treatment of dry eye after LASIK surgery. Ophthalmic Res 2018;60:80–6. https://doi.org/10.1159/000487951.

[41] Murtaza F, Toameh D, Chiu HH, Tam ES, Somani S. Autologous platelet-rich plasma drops for evaporative dry eye disease from meibomian gland dysfunction: a pilot study. Clin Ophthalmol 2022;16:2199–208. https://doi.org/10.2147/OPTH.S367807.

[42] Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Fernandez-Vega Cueto L, Anitua E, Begoña L, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. Int Ophthalmol 2018;38:1193–204. https://doi.org/10.1007/S10792-017-0582-7.

[43] Jones L, Downie LE, Korb D, Benitez-del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15:575–628.

[44] Alio LJ, Arnalich-Montiel FE, Rodriguez A. The role of "eye platelet rich plasma" (E-PRP) for wound healing in ophthalmology. Curr Pharm Biotechnol 2012;13:1257–65. https://doi.org/10.2174/138920112800624355.

[45] Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. Br J Ophthalmol 2004;88:1467–74. https://doi.org/10.1136/BJO.2004.044347.

[46] Hussain M, Shtein RM, Sugar A, Soong HK, Woodward MA, De Loss K, et al. Long-term use of autologous serum 50% eye drops for the treatment of dry eye disease. Cornea 2014;33:1245–51. https://doi.org/10.1097/ICO.0000000000000271.

[47] Wu TE, Chen CJ, Hu CC, Cheng CK. Easy-to-prepare autologous platelet-rich plasma in the treatment of refractory corneal ulcers. Taiwan J Ophthalmol 2015;5:132–5. https://doi.org/10.1016/J.TJO.2014.09.001.

[48] Bron AJ, Argüeso P, Irkec M, Bright FV. Clinical staining of the ocular surface: mechanisms and interpretations. Prog Retin Eye Res 2015;44:36–61. https://doi.org/10.1016/J.PRETEYERES.2014.10.001.
[49] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf 2017;15:539–74. https://doi.org/10.1016/j.jtos.2017.05.001.
[50] Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets 2013;24:173–82. https://doi.org/10.3109/09537104.2012.684730.
[51] López-Plandolit S, Morales MC, Freire V, Grau AE, Durán JA. Efficacy of plasma rich in growth factors for the treatment of dry eye. Cornea 2011;30:1312–7. https://doi.org/10.1097/ICO.0B013E31820D86D6.
[52] Núñez-Álvarez C, Osborne NN. Enhancement of corneal epithelium cell survival, proliferation and migration by red light: relevance to corneal wound healing. Exp Eye Res 2019;180:231–41. https://doi.org/10.1016/J.EXER.2019.01.003.
[53] Yu FSX, Yin J, Xu K, Huang J. Growth factors and corneal epithelial wound healing. Brain Res Bull 2010;81:229. https://doi.org/10.1016/J.BRAINRESBULL.2009.08.024.
[54] Arnalich F, Rodriguez AE, Luque-Rio A, Alio JL. Solid platelet rich plasma in corneal surgery. Ophthalmol Ther 2016;5:31. https://doi.org/10.1007/S40123-016-0051-9.
[55] Kim KM, Shin YT, Kim HK. Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis. Jpn J Ophthalmol 2012;56:544–50. https://doi.org/10.1007/S10384-012-0175-Y.
[56] Panda A, Jain M, Vanathi M, Velpandian T, Khokhar S, Dada T. Topical autologous platelet-rich plasma eyedrops for acute corneal chemical injury. Cornea 2012;31:989–93. https://doi.org/10.1097/ICO.0B013E3182114661.